REMARKS

Amendments to the Claims

Upon entry of this Amendment, claims 1-12, 15-16, and 29 are pending in the application. Applicants have cancelled claims 13-14, 17-28, and 30-39 without prejudice to further prosecution. Applicants reserve the right to pursue the subject matter of the cancelled claims. Applicants will submit a further Supplemental Preliminary Amendment adding new claims in due course.

Amendments to the Specification

Applicants have amended various paragraphs on pages: 1, 4, 7, 8, 31, 32 and 36.

Page 1, lines 6-11

Applicants added the claim of priority to the International Application from which the current national application is based.

Page 4, lines 1-5

Applicants amended page 4, ll. 1-5 of the Background section to correct an inadvertent error. The statement originally read, "Recently, Nicchitta et al., WO 01/72779 (PCT/US01/09512), demonstrated that HSP90 can assume a different conformation upon heat shock and/or binding by the fluorophore bis-ANS. Specifically, Nicchitta et al. demonstrated that this induced conformation exhibits ***a higher affinity for certain HSP90 ligands*** than for a different form of HSP90 that predominates in normal cells." Emphasis added.

The statement that the induced conformation exhibits a higher affinity for the HSP90 ligands is inaccurate. To clarify the teaching of Nicchitta et al., Applicants have amended the sentences to read, "Recently, Nicchitta et al., WO 01/72779 (PCT/US01/09512), disclosed that GRP94 (an endoplasmic reticulum paralog of the

Hsp90 family of chaperones) can assume a different conformation upon treatment with heat shock and/or binding by the fluorophore bis-ANS. Specifically, Nicchitta et al. indicated that this induced conformation exhibits stimulated polypeptide binding and chaperone activities relative to those exhibited by a different form of GRP94 that predominates in normal untreated GRP94."

Nicchitta et al., WO 01/72779 (PCT/US01/09512), teaches that GRP94 can assume an active conformation wherein its chaperone and polypeptide (substrate) binding activities are markedly stimulated or inhibited. This conformational change can be induced by ligand binding to its N-terminal nucleotide binding domain of GRP94. Nicchitta et al., p. 16, ll. 8-20. Nicchitta et al. further discloses that the confirmational change may also be induced by either heat shocking or by binding with bis-ANS. Nicchitta et al., p. 40, ll. 4-9 and p. 43, ll. 6-8. Therefore, Nicchitta et al. only teaches that the induced conformation of GRP94 exhibits different peptide binding and chaperone activities than a normal untreated form of GRP94; Nicchitta et al. does not teach that the induced active conformation of GRP94 exhibits a higher affinity for non-peptide ligands, which bind to its N-terminal nucleotide binding domain.

Accordingly, Applicants respectfully request the entry of the amendment to page 4, ll. 1-5 of the Specification in order to accurately describe the teachings of the Nicchitta reference. A copy of Nicchitta et al. is enclosed herein.

Page 7, lines 26-28

Applicants amended the description of Figure 4 to highlight for the readers the fact that the "purified HSP90" is a "purified native form" of HSP90. Figure 4 illustrates the results obtained in Example 5 which unambiguously states that "purified native HSP90" was used in the experiments. Therefore, adding the term "native" to describe the purified HSP90 in the description of Figure 4 does not add new matter.

Page 7, lines 29-30

Applicants amended the description of Figure 5 to correct an inadvertent error. The original description of Figure 5 does not reflect the results reported in the figure, and

hence necessitates the amendment.

Figure 5 includes two graphs and a table. The graphs show the % inhibition binding of 17-AAG to HSP90 from the specific high Her-2 expressing cells: SKOV-3, SKBR-3 and N87; heat-shocked HSP90; bis-ANS treated HSP90 and HSP90 from normal cells (recombinant native HSP90, Fibroblasts, RPTEC, hPBMC). The Table lists the IC_{50} values (the concentration of 17-AAG needed to cause half-maximal inhibition of binding). A literal interpretation of the IC_{50} values in the Table would show that 17-AAG has a higher apparent binding affinity for HSP90s from the specific high Her-2 expressing cells: SKOV-3, SKBR-3 and N87 ($IC_{50} < 10$), and for heat-shocked HSP90 ($IC_{50} = 20$) and bis-ANS treated HSP90 ($IC_{50} = 40$), than for HSP90 from normal cells ($IC_{50} = 400$-1000). The amended description conveys this interpretation.

Since the amendment just restates results that are reported in Figure 5 as originally presented, no new matter has been added.

Page 8, lines 1-3

Similarly, the description of Figure 6 is amended to better explain the data displayed in the Figure. The amendment captures information that is fully disclosed in Example 5; therefore, no new matter is added by the amendment.

Page 31, line 27 to page 32, line 13

Applicants have added the term "heat" to modify the "shocked HSP90" on page 32, line 10. The phrase which follows describes the preparation of the HSP90 by incubating for 15 mins. at 90 °C. The term "heat-shocked HSP90" appears in the description of Figure 5 (p. 7, l. 31) and also in the legend of Figure 5. The modifier was inadvertently left out in this paragraph, no new matter has been added by the amendment.

Page 32, lines 1-31

Applicants have punctuated (added colons) to the sentences which describe the mobile phases. The amendment is made to add clarity, no new matter has been added.

Page 36, lines 1-3

Applicants have rearranged the columns of the table to group the test results according to the test cell types. The amendment is made to add clarity, no new matter has be added.

Amendment to the Drawing

Applicants have replaced the originally filed Figure 1. In the originally filed application, the same graph is presented as both Figure 1 and Figure 2. The error is inadvertent and obvious. The originally filed Figure 1 reports an experiment that was performed in wells B4, C4, D4, E4, F4 and G4 of a 96-well plate. However, the Specification indicates that Figure 1 should report an experiment that was performed in wells B3, C3, D3, E3, F3 and G3, and Figure 2 should report an experiment that was performed in wells B4, C4, D4, E4, F4 and G4 of a 96-well plate. (See, Example 4, p. 30, l. 11 to p. 31, l. 25) Applicants submit, because the experiments are fully described in Example 4 as originally filed, substituting the correct graph in Figure 1 does not introduce new matter.

CONCLUSION

Applicants have made amendments to the Claim, the Specification and to the Drawing, and no new matter has been added by the amendments. Accordingly, Applicants respectfully request the entry of the amendments.

The Commissioner is authorized to charge the fee for National Filing this Application, which is believed to be $ 705.00, as well as any fee required by this submission to our Deposit Account No. 50-2613.

Respectfully submitted,
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